UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/012,846	01/23/1998	MARC F. CHARETTE	CIBT-P01-510	2619

28120 7590 06/18/2002

ROPES & GRAY
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

EXAMINER
TURNER, SHARON L

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 06/18/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/012,846	Applicant(s) Charette
	Examiner Sharon L. Turner, Ph.D.	Art Unit 1647

-- Th MAILING DATE of this communication app ars on the cover sheet with th correspondence address --

Period for R ply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on 3-5-02

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 28-51 is/are pending in the applica

4a) Of the above, claim(s) 33-45 and 49-51 is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 28-32 and 46-48 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☒ Claims 28-51 are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Response to Amendment

1. Claims 28-51 are pending.

Election/Restriction

2. Claims 28, 33-36, 37, 38 and 43-45, drawn to the extent of BMP-2, BMP-5, BMP-6 and 60A stand withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 18. However it is presently noted that the group is an improper Markusch as there is no common core structure essential to the recited utility and thus the species are in fact distinct Groups. There is no indication of an allowable generic claim. The prior art rejections of record are maintained as set forth below.

3. Newly submitted claims 37-42 and 49-51 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: The new invention is directed to a method for reducing memory dysfunction associated with damaged hippocampal tissue. Applicants are referred to point 2, page 2 of the previous action, Paper No. 19, mailed 8-21-01 where it was set forth that a return to such subject matter would be considered as nonelected. In particular, the endpoints which comprise the preamble of the claims and which bear patentable weight differ each from the other and thus define distinct methods with different endpoints or effects to be achieved. As a method for restoring a function of damaged hippocampal tissue and a method for reducing memory dysfunction are distinct as recognized in the art, see in particular, the inventions as claimed are distinct each from the other.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 37-42 and 49-51 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claim Objections

4. Claim 28 stands objected to as reciting an improper Markush Group. M.P.E.P. 803.02 states that:

> "Since the decisions in In re Weber **,198 USPQ 328 (CCPA 1978); and In re Haas, 198 USPQ 334 (CCPA 1978), it is improper for the Office to refuse to examine that which applicants regard as their invention, unless the subject matter in a claim lacks unity of invention, In re Harnish , 631 F.2d 716, 206 USPQ 300 (CCPA 1980); Ex Parte Hozumi , 3 USPQ2d 1059 (Bd. Pat. App. & Int. 1984). Broadly, unity of invention exists where compounds included within a Markush group (1) share a common utility and (2) share a substantial structural feature disclosed as being essential to that utility."

Applicants argue essentially that the 89% sequence conservancy in the C-terminal seven cysteine domain as shown in Figure 1, represents a sufficient common structural feature essential to the utility of enhancing the formation and development of dendrites and synapses in hippocampal cells. It is noted that the C-terminal seven cysteine domain of human OP-1 corresponds to residues 330-431 of SEQ ID NO:2, as disclosed in the specification at p. 18, lines 21-23.

Applicant's arguments filed 3-5-02 have been fully considered but are not persuasive. In particular Applicants are referred to the enablement rejection of record. The specification

provides no evidentiary support for conserved activity of the morphogens claimed, in particular for BMP-2, BMP-5, BMP-6 and 60A or for the recited portions of OP-1, SEQ ID NO:2 as claimed in providing for the formation or development of dendrites and synapses in hippocampal cells, and the artisan would have reason to doubt the unsubstantiated allegation as set forth below.

Rejections Maintained

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claim 28 stands rejected as set forth in Paper No. 19, mailed 8-21-01, under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The specification discloses SEQ ID NO: 2 which corresponds to the full length mature OP-1 of undisclosed species (at least mouse and human are known). This SEQ ID NO meets the written description provisions of 35 USC 112, first paragraph. However, the claims are directed to or encompass the generic recitation of all representative OP-1, BMP-2, BMP-5, BMP-6 and 60A proteins corresponding to sequences from alternative species, mutated sequences, allelic and

splice variants, which sequences differ in identity from the disclosed peptides as set forth in the specification. Thus, none of these sequences meets the written description provision of 35 USC 112, first paragraph because the specification fails to describe any alternative species, mutated, allelic or splice variants of OP-1, BMP-2, BMP-5, BMP-6 and 60A other than those described as set forth above.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that, "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is for purposes of the 'written description' inquiry, whatever is now claimed." (See Vas-Cath at page 1116.)

With the exception of SEQ ID NO:2 of the instant application, the skilled artisan cannot envision the detailed chemical structure of the encompassed amino acids and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The specific amino acids are required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Therefore, only SEQ ID NO: 2 of the instant application, but not the full breadth of claims meet the written description provision of 35 USC 112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

Applicants argue that the morphogens are known and well characterized in the art as referenced, see Response, p. 6 and that therefore there is not need to further describe that known by the artisan. Applicants further note that the claims are directed to methods and not compositions and thus that the cases cited are not relevant to the application.

Applicant's arguments filed 5-3-02 have been fully considered but are not persuasive. While the prior art discloses for example SEQ ID NO:2 which is OP-1, etc., it is noted that the breadth of the claims are broader than that disclosed as referenced. In particular, the claims are directed to the generic compounds and not to the specific species disclosed in the prior art. For example, SEQ ID NO:2 is disclosed as a particular allele of human OP-1. However, the generic recitation encompasses allelic and functional variants as contemplated in the specification. These sequences exhibit alternative sequences, portions and sequences from alternative species, for example frog OP-1 which are encompassed by the generic recitation of the claim, but which are not disclosed by the specification and are not recognized in the prior art. Thus, the generic recitations lack adequate written description. While the claims are directed to methods, it is noted that the methods require the compositions and thus the requirements for a full description of the compositions required by the method must be provided to comply with the written

description requirements and thus the case law pertaining to the description of compositions in general is relevant and pertinent to the full scope of the method claims which require the use of the compositions as claimed.

7. Claims 28-31 stand rejected as set forth in Paper No. 19, mailed 8-21-01 and as set forth herein, and new claims 46-48 are newly rejected as necessitated by amendment for the same reasons of record and as set forth herein, under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for accelerated dendritic outgrowth of hippocampal neurons in culture in the presence of OP-1 as disclosed at p. 61, lines 1-7, does not reasonably provide enablement for the invention as generically claimed, in particular for the alternative morphogens recited, including portions of SEQ ID NO:2, for enhancing the formation and development of dendrites and synapses in hippocampal cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicants argue with respect to the amended invention that it is not their requirement to provide working examples for all embodiments of the invention including of alternative morphogens and in vivo paradigms, and that alternative uses are not evidence which would cast doubt on the effectiveness of their invention.

Applicant's arguments filed 5-3-02 have been fully considered but are not persuasive. While it is not a requirement to provide a working embodiment for every aspect of the invention, it is a requirement that applicants convey enough guidance that the artisan is readily assured of

the ability to make and use the invention as claimed. In the instant case the specification provides a single exemplification of SEQ ID NO:2, human OP-1 induced formation and development of dendrites and synapses in hippocampal cells in vitro. The guidance of the specification is thus limited to the exemplification of a single species, which is not representative to the genus of molecules claimed. The specification provides no nexus whereby the artisan could conclude that any other morphogen or portion thereof would be sufficient to provide for the functional activities claimed. In addition, as previously noted, determination of a proteins function based solely upon structural similarity to other peptides is unpredictable in the art. Thus, the artisan would have sufficient reason to doubt the unsubstantiated teachings of the specification absent further guidance and/or evidentiary support. Note the previous grounds of rejection.

It is noted that the previous grounds of rejection pertaining to a lack of enablement for enhancing the formation and development of dendrites and synapses in hippocampal cells, specifically in vivo, has been withdrawn based on the enablement provided by WO 94/03200 and WO 95/05846 which references teach in vitro and in vivo neuronal regeneration. Thus, the references appear to be enabling for both in vitro and in vivo enhancement of formation and development of dendrites and synapses in CNS neurons, inclusive of hippocampal cells.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 28-32 stand rejected and new claims 46-48 are rejected as necessitated by amendment for the same reasons of record as set forth in Paper No. 19, mailed 8-21-01, and as set forth herein under 35 U.S.C. 102(b) as being anticipated by Reuger et al., WO9403200, 17 February 1994.

Reuger et al., teach morphogen-induced nerve regeneration and repair of damaged neurons and neuronal pathways, see in particular abstract. The subject morphogen includes human and mouse species of OP-1, disclosed as SEQ ID Nos:5 and 6 which share identity with instant SEQ ID NO:2. Reuger et al., teaches OP-1 enhancement of neuronal cell survival, see in particular Example 3, p. 79-81, redifferentiation which includes neuronal cell outgrowth, see in particular Figure 1B, protection from chemical trauma, see in particular Example 5, p. 84-85, nerve-gap repair, see in particular p. 90-93, alleviation of immune response-mediated damage, Example 10, p. 97-99 and repair of neural pathways, see in particular claims 32-33. As the reference teachings of Reuger comprise repairing damaged neurons with OP-1 wherein the treatment comprises contacting neural cells with OP-1 and repairing damaged cells and pathways, the reference teachings and treatment inherently provide for dendritic outgrowth and synapse formation of the claimed hippocampal neurons. In particular, the treatment of Reuger includes delivery of OP-1 to hippocampal neurons to stimulate neural regeneration, see in particular p. 100. As neural regeneration is recognized to provide for the recovery of dendrite

and axonal projections and establish synapses, the reference teachings anticipate the claimed invention. It is also noted that the Reuger invention is specifically recognized for the treatment of Alzheimer's Disease where hippocampal cells are recognized to be affected by neuronal degeneration. Reuger clearly teaches that OP-1 administration is effective to stimulate CNS regeneration as disclosed for example in Example 3 and Example 7. Further, it is noted that all that is required to achieve the elements recited in the preamble are "contacting said cells with a morphogen as recited, i.e., comprising SEQ ID NO:2 or a portion of SEQ ID NO:2. Reuger teaches contacting hippocampal cells with OP-1 in particular at p. 100 and additionally results in such contact as achieved by both in vitro and in vivo administration. Thus, the Reuger teachings are necessarily anticipatory as the methods of contacting are the same. Therefore, the Reuger teachings anticipate the claimed invention.

Applicants argue that Reuger relates to methods for enhancing survival of neural cells and acknowledges that enhancing survival would be expected to maintain memory by inhibiting further loss of neuronal cells.

Applicant's arguments filed 3-5-02 have been fully considered but are not persuasive. It is noted that all that is required to achieve the elements recited in the preamble are "contacting said cells with a morphogen" as recited, i.e., comprising SEQ ID NO:2 or a portion of SEQ ID NO:2. Reuger teaches contacting hippocampal cells with OP-1 of SEQ ID NO:2, in particular at p. 100 and additionally results in such contact as achieved by both in vitro and in vivo administration. Thus, the Reuger teachings are necessarily anticipatory as the methods of

contacting are the same. Therefore, the Reuger teachings necessarily anticipate the claimed invention and inherently provide the noted characteristics of enhancing formation and development of dendrites and synapses in hippocampal cells.

10. Claims 28-32 stand rejected and new claims 46-48 are rejected as necessitated by amendment for the same reasons of record as set forth in Paper No. 19, mailed 8-21-01, and as set forth herein under 35 U.S.C. 102(b) as being anticipated by Wang et al., WO9505846, 2 March 1995.

Wang et al., teach neural regeneration, growth and repair of damaged neural tissue using the morphogen BMP-7 which is identical to OP-1 as referenced in US 5,141,905, see in particular abstract. The method of treatment comprises contacting the neural cells with the BMP-7(OP-1) for example as claimed in claim 13-14 and 21 and provides treatment of damaged neural tissue. The treatment is specifically anticipated for the treatment of Alzheimer's as disclosed at p. 5, lines 5-14, in particular. Alzheimer's is a disease readily recognized in the art to be associated with degeneration of hippocampal neurons and thus treatment with OP-1 would be recognized for neural regeneration in hippocampal tissue. It is noted that all that is required to achieve the elements recited in the preamble are "contacting said (hippocampal) cells with a morphogen as recited, i.e., comprising SEQ ID NO:2 or a portion of SEQ ID NO:2. Wang et al., teaches contacting neural cells including at the site of said defect or damage with BMP-7, see in particular claims 8, 13 and 21. The administration may also be intravenously, for example, p. 8, lines 3-8 and thus results in such contact achieved by in vivo administration. The Wang

teachings are necessarily anticipatory as the methods of contacting are the same. Therefore, the Wang teachings anticipate the claimed invention and inherently provide for dendritic outgrowth and synapse formation in hippocampal cells as is instantly claimed. Thus, the reference teachings anticipate the claimed invention.

Applicants argue that the Wang reference discloses growth of neural cells and that the idea that such treatment would inherently result in dendritic outgrowth or synapse formation is purely speculative.

Applicant's arguments have been fully considered but are not persuasive. In particular the treatment steps of contacting hippocampal cells with OP-1 is achieved by treatment of the CNS with OP-1 as disclosed by Wang. Thus, as the treatments are the same, the effects logically flow and thus are inherent to the Wang reference which produces neural regeneration in the CNS and treatment of Alzheimer's Disease as disclosed. It is applicant's burden to distinguish the method and/or show non-obviousness.

Rejections Necessitated by Amendment

11. Claims 46-48 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claims 46-48 recite morphogens comprising residues 292-330, 292-431 and 30-431 of SEQ ID NO:2. However, Applicants have neglected to point to where in the specification

support for such recitation may be found and the Examiner is unable to find such support. Thus, absent evidentiary support for the recitation, the newly recited residues constitute new matter.

Status of Claims

12. No claims are allowed.

Conclusion

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

14. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (703) 308-0056. The examiner can normally be reached on Monday-Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached at (703) 308-4623.

Sharon L. Turner, Ph.D.
June 4, 2002

Gary L. Kunz

GARY L. KUNZ
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600